Editorial Comment

Acta Haematologica

Acta Haematol 2019;142:195–196
DOI: 10.1159/000501442

Received: June 4, 2019
Accepted: June 10, 2019
Published online: July 17, 2019

Towards New Frontiers of Direct Oral Anticoagulants: Sickle Cell Disease

Andrea Boccatonda Francesca Santilli

Department of Medicine and Aging and Center of Aging Science and Translational Medicine (CESI-Met), G. d'Annunzio University of Chieti, Chieti, Italy

Editorial comment on the paper by Ameet Patel et al. Decreased Bleeding Incidence with Direct Oral Anticoagulants Compared to Vitamin K Antagonist and Low-Molecular-Weight Heparin in Patients with Sickle Cell Disease and Venous Thromboembolism. Acta Haematol 2019;142:233–238

New oral anticoagulants or direct oral anticoagulants (DOACs) are no longer such "new" drugs, as for about 15 years a lot of studies have shown their effectiveness, especially in patients with atrial fibrillation and venous thromboembolism (VTE). Although differences exist between one molecule and another, data in the literature show a lower rate of hemorrhagic complications in the face of a similar, or even increased in some cases, anticoagulant capacity with respect to "old" vitamin-K antagonist.

Recent data about DOACs concern their new applications, such as the experimentation of these molecules in primary or secondary prevention to special categories of high-risk thrombotic patients due to different pathologies and disease. The study by Patel et al. [1] investigates the use of DOACs in secondary prevention for thromboembolism in patients affected by sickle cell disease (SCD), a not well-investigated specific category of high-thrombotic risk patients.

Over the last years, SCD has gotten more and more prominence as a risk factor for thrombosis, as the presence of more early and effective diagnostic tools and treatments has increased the life expectancy of these patients, thus leading to a greater number of organ complications. On the one hand, SCD is a primary disease of erythrocytes due to abnormal polymerization of hemoglobin tetramers. On the other hand, the activation of prothrombotic factors and/or decreasing antithrombotic proteins lead to an abnormal hypercoagulability [2]. VTE is reported approximately in 12% of the patients with SCD by 40 years of age, at least in part as a result of hypercoagulable state [3]. Sickle variant genotypes confer a higher risk of non-catheter-related VTE in comparison with sickle cell anemia genotypes (SS/Sβ(0)) [3]. Furthermore, VTE recurrence in SCD patients is related to increased mortality [3]. Notably, current recommendations on the management of SCD patients with VTE are not different from those for other adults [4], and there is no clear evidence that anticoagulant prescription should differ from that of other patients.

In their study, Patel et al. [1] demonstrated a comparable efficacy among three examined anticoagulant classes (vitamin-K antagonist, low-molecular-weight heparin, and DOACs), with a lower incidence of significant bleeding with DOACs, thereby supporting the utilization of a DOAC to treat initial VTE in patients with SCD.

DOAC prescription is conditioned by several factors increasing the bleeding risk, such as age, cancer, renal and liver failure, thrombocytopenia, diabetes, antiplatelet, and nonsteroidal anti-inflammatory drugs [4]. In the work by Patel et al. [1], most of these factors are part of the exclusion criteria; therefore, recruited patients seem to present a baseline low bleeding risk. In particular, the preliminary evaluation of renal function is of primary importance in SCD patients who develop chronic kidney disease in 1/3 of the cases and progress to end-stage renal disease in 4–18% of them [5]. Furthermore, the estimation of cre-

E-Mail karger@karger.com
www.karger.com/aha

Andrea Boccatonda
Department of Medicine and Aging and Center of Aging Science and Translational Medicine (CESI-Met), G. d'Annunzio University of Chieti
Via dei Vestini, IT–66100 Chieti (Italy)
E-Mail andrea.boccatonda@gmail.com

atinine clearance thresholds is linked to a different prescription of drugs, even within the same class of DOACs, in which some molecules can be administered with reduced dosages depending on the renal functionality values [6]. However, estimation of the glomerular filtration rate by serum creatinine can be inaccurate in SCD patients, thereby suggesting the utilization of new biomarkers such as cystatin C, when available [5]. Another major concern is represented by the optimal length of anticoagulation in patients with SCD who develop VTE [2]. The main question is whether SCD should be considered a persistent risk factor for recurrent VTE requiring indefinite anticoagulation after the first VTE event or a mild thrombophilia, with a shorter duration of secondary pharmacological prophylaxis. In the work by Patel et al. [1], the proportion of patients with recurrent VTE at a median follow-up of 11.8 months is almost 30%. In addition, the presence of an indwelling central venous catheter has been correlated with a 25% incidence of VTE in patients with SCD [1]. Therefore, a provoked VTE in a patient with SCD may be associated with a much higher risk of recurrence than in the general population. On the other hand, anticoagulation duration is determined by weighing the risk of recurrent VTE against the risk of major bleeding. Some reports point at an increased bleeding risk in SCD patients on anticoagulation for VTE in comparison to the general population, even without other known risk factors. Data from Naik et al. [3] demonstrate a high cumulative incidence of major bleeding of 2.9% at 6 months and 5.0% at 1 year in SCD patients after incident VTE. These data may suggest considering SCD patients to belong to the moderate-to-high-risk-for-bleeding category.

In conclusion, DOACs seem to be the optimal choice to treat and prevent recurrent VTE in SCD patients, due to their comparable efficacy among other anticoagulant drugs and the lower incidence of significant bleeding [1]. However, it must be emphasized that the data are retrospective and were obtained from a low-risk population with few comorbidities. Prospective randomized controlled studies are needed to better identify the best thromboprophylactic therapy for SCD patients. In particular, the optimal duration of therapy, dose changes in relation to renal function, and the prescription of anticoagulant therapy in specific categories of patients, such as indwelling central venous catheter carriers and pregnant women, still remain open questions to investigate.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

Boccatonda A. contributed to the design of the editorial, analysis of the more relevant literature, drafting of the manuscript, and critical revision for important intellectual content. Santilli F. contributed to the design of the editorial, drafting of the manuscript, and critical revision for important intellectual content.

References

1 Patel A, Williams H, Baer MR, Zimrin AB, Law JY. Decreased Bleeding Incidence with Direct Oral Anticoagulants Compared to Vitamin K Antagonist and Low-Molecular-Weight Heparin in Patients with Sickle Cell Disease and Venous Thromboembolism. Acta Haematol. DOI: 10.1159/000500223.

2 Pakbaz Z, Wun T. Role of the hemostatic system on sickle cell disease pathophysiology and potential therapeutics. Hematol Oncol Clin North Am. 2014 Apr;28(2):355–74.

3 Naik RP, Streiff MB, Haywood C Jr, Segal JB, Lanzkron S. Venous thromboembolism incidence in the Cooperative Study of Sickle Cell Disease. J Thromb Haemost. 2014 Dec; 12(12):2010–6.

4 Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb;149(2):315–52.

5 Airy M, Eknoyan G. The kidney in sickle hemoglobinopathies. Clin Nephrol. 2017 Feb; 87(2017)(2):55–68.

6 Sciascia S, Radin M, Schreiber K, Fenoglio R, Baldovino S, Roccatello D. Chronic kidney disease and anticoagulation: from vitamin K antagonists and heparins to direct oral anticoagulant agents. Intern Emerg Med. 2017 Dec; 12(8):1101–8.